# Stochastic phenomena in the dynamical tumor-immune system

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Irina Bashkirtseva

# Stochastic Phenomena in the Dynamical Tumor-Immune System

Irina Bashkirtseva

*Department of Theoretical and Mathematical Physics, Ural Federal University, Lenina, 51, 620000, Ekaterinburg, Russia*

Irina.Bashkirtseva@urfu.ru

**Abstract.** A nonlinear dynamical model describing the interaction of tumor and immune cells is considered. Regimes of "dormant tumor" and "tumor explosion" are studied by methods of the bifurcation theory and stochastic simulation. Noise-induced transitions from "dormant tumor" to "tumor explosion" and back are investigated parametrically in dependence of the noise intensity and parameter of the inactivation of immune cells by tumor ones. Three scenarios of the noise-induced transitions are discussed: (i) from "dormant tumor" to "tumor explosion", (ii) from "tumor explosion" to "dormant tumor", (iii) oscillations between these two regimes.

## INTRODUCTION

Currently, the interest of mathematicians, engineers and biologists is attracted by the problem of control for complex biological systems of various levels. It can be both large-scale ecological systems and thin intracellular mechanisms. One of the most important tasks here is to solve the problem of targeted impact on the dynamics of tumor cells.

The competitive interaction between tumor cells and the effector (immune) cells is extremely complicated, so the elaboration of the appropriate mathematical models and constructive methods of their analysis is highly attractive [1, 2, 3, 4]. An influence of inevitable stochastic disturbances on models of tumor-immune interaction is a subject of recent investigations [5, 6, 7].

In the present paper, we study a dynamical model [8] of the tumor-immune system interaction under the stochastic disturbances. Phenomena of the noise-induced suppression and growth of tumor cells are investigated. Understanding probabilistic mechanisms of these phenomena can be achieved on the basis of the bifurcation analysis, description of the coexisting attractors and separatrices dividing their basins. We show how stochastic phenomena in this model can be investigated with the help of the parametric analysis of the noise-induced transitions between attractors. A constructive approach to the control of such stochastic transitions is discussed.

### Deterministic dynamics

As an initial base deterministic model of the dynamic interaction of immune effector cells and tumor cells we use the following system of nonlinear differential equations suggested in [8]:

$$\begin{aligned} \dot{x} &= \sigma + \rho\frac{xy}{\eta + y} - \mu xy - \gamma x \\ \dot{y} &= \alpha y(1 - \beta y) - xy. \end{aligned} \tag{1}$$

In [8], all biological details can be found. In system (1), $x$ is the density of effector cells and $y$ is the density of tumor cells in the zone of their interaction, the parameter $\sigma$ is the influx rate of effector cells into the region where tumor cells are localized, the term $\rho\frac{xy}{\eta + y}$ describes the stimulation of the immune system by tumor cells with tumor specific antigens. It is supposed that this stimulation of the immune system by tumor cells depends directly on the quantity

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of tumor cells with positive constants $\rho$ and $\eta$. The constant $\mu$ stands for the rate of the inactivation of immune cells by the tumor cells, the parameter $\gamma$ is the rate of the natural mortality of immune cells. The first term of the second equation in system (1) reflects the standard logistic low of the growth of the isolated population of tumor cells with the growth rate $\alpha$ and carrying capacity $1/\beta$. The second term of the second equation in system (1) models a destruction of tumor cells by the immune cells.

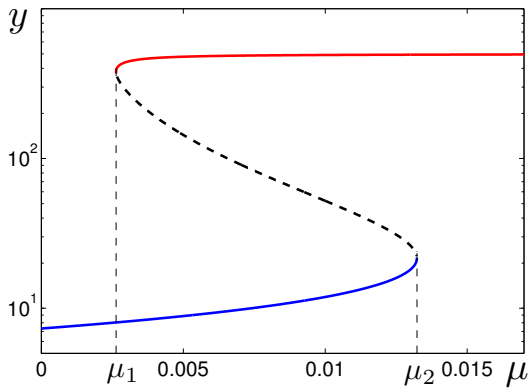


**FIGURE 1.** Equilibria of system (1) corresponding to tumor "dormancy" (blue) and "explosion" (red). The unstable equilibrium is shown by dashed line. Here, $\mu_1 = 0.002633,\ \mu_2 = 0.01323$.

In this non-dimensional model (1), we follow [8] and fix the parameters

$$\sigma = 0.1181,\ \gamma = 0.3743,\ \rho = 1.131,\ \eta = 20.19,\ \alpha = 1.636,\ \beta = 0.002.$$

In [8], these parameters were estimated in experiments. In this paper, we consider $\mu$ as a bifurcation parameter which plays an important role in the nonlinear dynamical interaction of immune and tumor cells. In this section, we study how the variation of $\mu$ in the interval $0 < \mu < 0.2$ changes the dynamics of system (1).

The system (1) has the equilibrium $(\frac{\sigma}{\gamma}, 0)$ that is unstable for the considered set of parameters. Coordinates $(x, y)$ of non-trivial equilibria of system (1) satisfy the system

$$x = \alpha(1 - \beta y)$$
$$\sigma + \left(\rho\frac{y}{\eta + y} - \mu y - \gamma\right)\alpha(1 - \beta y) = 0.$$

For system (1), $y$-coordinates of non-trivial equilibria are plotted in Figure 1 versus the parameter $\mu$. Here, one can see two stable equilibria (red and blue lines), and the unstable equilibrium (dashed). The equilibrium with the smaller value of $y$ (blue) will be referred as $D$ because this regime models of the "dormant tumor" when the immune system provides a relatively low level of tumor cells. In contrary, he equilibrium with the larger value of $y$ (red) will be referred as $E$. This stable equilibrium characterized by a high level of tumor cells and low level of effector cells corresponds to the another dynamic regime of so-called "tumor explosion".

In deterministic system (1), two points of the saddle-node bifurcation can be determined: $\mu_1 = 0.002633,\ \mu_2 = 0.01323$ (see Figure 1). The equilibrium $D$ is stable in the interval $0 < \mu < \mu_2$ whereas the equilibrium $E$ is stable in the interval $\mu_1 < \mu < 0.2$. In the interval $\mu_1 < \mu < \mu_2$, the system is bistable and has one more equilibrium $S$ (dashed line) that is unstable. In this parametric region, a behavior of system (1) depends on the initial data.

In Figure 2, phase portraits of system (1) are shown for some values of the parameter $\mu$.

In the parametric zone $0 < \mu < \mu_1$, the stable equilibrium $D$ is the single attractor of system. So, the immune system keeps the tumor in dormancy independently on the initial quantity of tumor and effector cells (see Figure 3a for $\mu = 0.0026 < \mu_1 = 0.002633$).

In the interval $\mu_1 < \mu < \mu_2$, system is bistable and basins of attraction of stable equilibria $D$ and $E$ ($D$-basin and $E$-basin) are separated by the separatrix. The role of such a separatrix is played by the stable manifold of the saddle point $S$ shown by the empty circle. The separatrices are plotted by green dashed lines in Figures 2b,c,d,e for

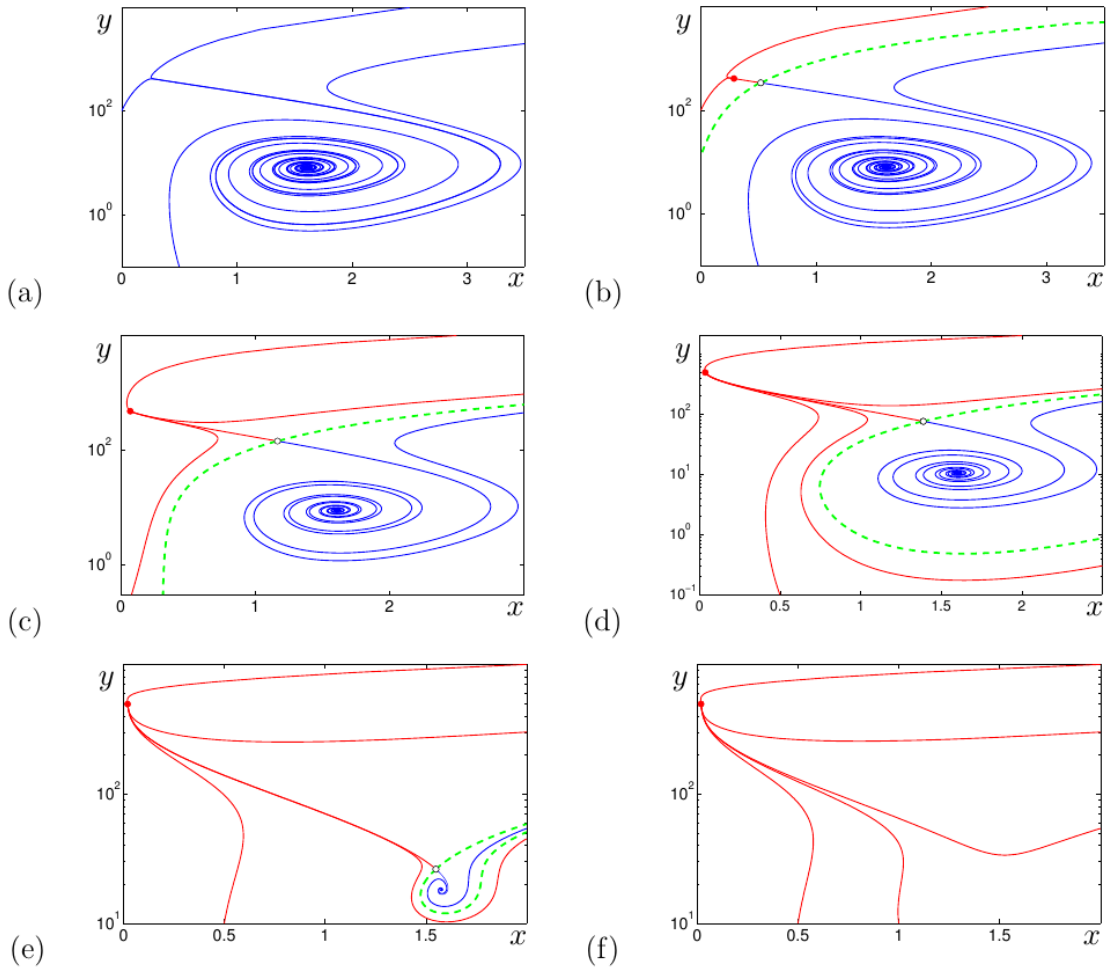


**FIGURE 2.** Phase portraits of the deterministic system (1) for (a) $\mu = 0.0026$, (b) $\mu = 0.0027$, (c) $\mu = 0.005$, (d) $\mu = 0.008$, (e) $\mu = 0.013$, (f) $\mu = 0.014$. The separatrix between basins of tumor "dormancy" (blue) and tumor "explosion" (red) is shown by green dashed line.

parameters $\mu = 0.0027$, $\mu = 0.005$, $\mu = 0.008$, and $\mu = 0.013$ correspondingly. In the bistability zone $\mu_1 < \mu < \mu_2$, the immune system is rather active and provides the stable regime of the "dormant tumor" only if the initial values of tumor and effector cells belong to the $D$-basin (see Figures 3b-e). As can be seen when the parameter $\mu$ tends to the bifurcation value $\mu_2$, the $D$-basin decreases and collapses at $\mu = \mu_2$.

In the monostable parametric zone $\mu_1 < \mu < 0.2$, the system exhibits "tumor explosion" for any initial data (see Figure 3f).

In the next section, we will show how the inevitable random disturbances can deform tumor-immune system dynamics in the bistability zone.

## Stochastic dynamics

Let us consider the immune-tumor system with random disturbances:

$$\begin{aligned} \dot{x} &= \sigma + (\rho + \varepsilon\xi(t))\,\frac{xy}{\eta + y} - \mu xy - \gamma x \\ \dot{y} &= \alpha y(1 - \beta y) - xy. \end{aligned} \tag{2}$$

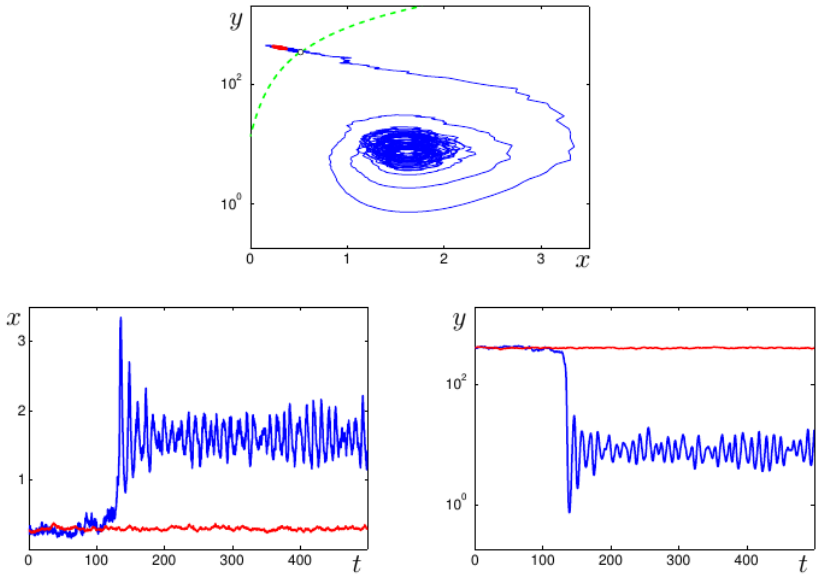


**FIGURE 3.** Phase trajectories and time series of stochastic system (2) for $\mu = 0.0027$ with $\varepsilon = 0.05$ (red) and $\varepsilon = 0.2$ (blue).

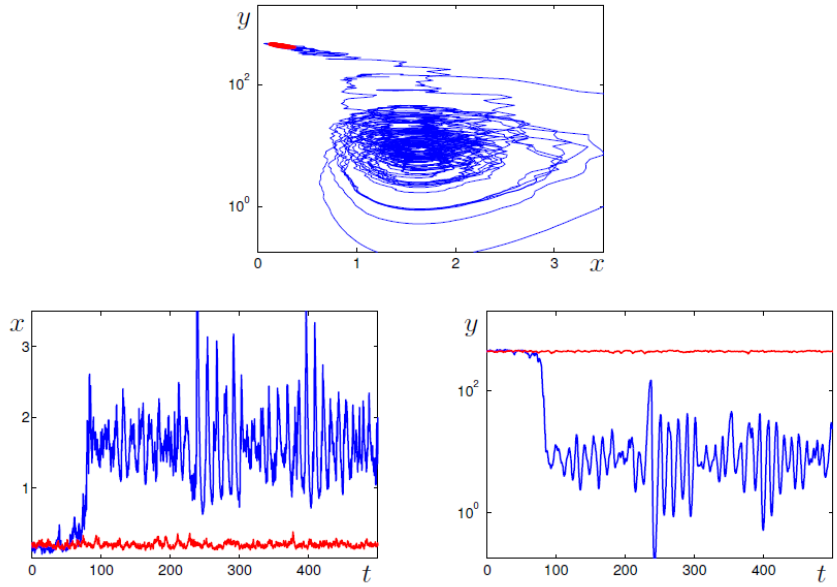


**FIGURE 4.** Phase trajectories and time series of stochastic system (2) for $\mu = 0.003$ with $\varepsilon = 0.2$ (red) and $\varepsilon = 0.4$ (blue).

Here, uncorrellated Gaussian white noise $\xi(t)$ models random fluctuations of the parameter $\rho$ that stands for the activation of the immune system by tumor cells. In system (2), $\mathrm{E}\xi(t) = 0$, $\mathrm{E}\xi(t)\xi(\tau) = \delta(t-\tau)$, and $\varepsilon$ is the noise intensity.

Consider stochastic system (2) in the bistability zone. Let us compare the system behavior for various values of $\mu$ and $\varepsilon$. Results of the numerical simulations are shown in Figures 3-8.

In Figure 3 for $\mu = 0.0027$, two solutions of system (2) starting from the equilibrium $E$ ("tumor explosion") are plotted for different noise intensities. For smaller noise ($\varepsilon = 0.05$, red colour), the random trajectory oscillates near

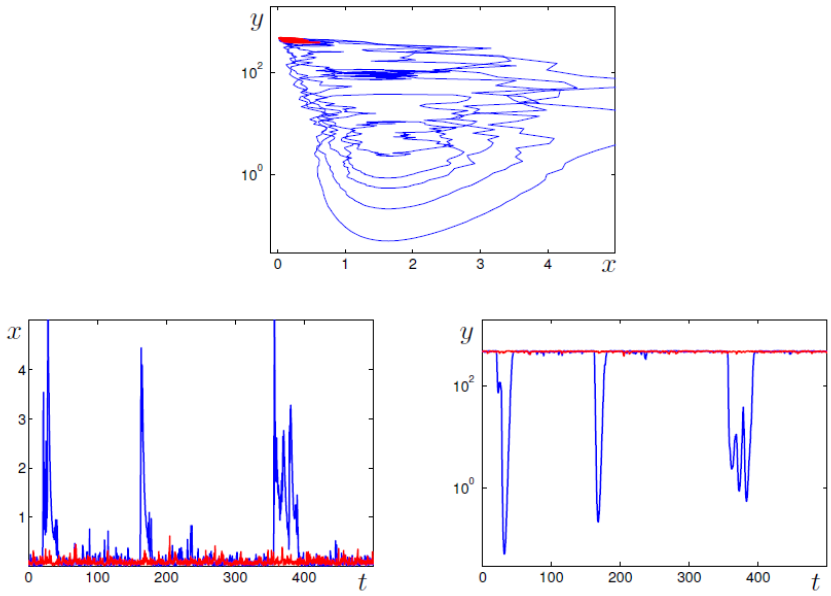


**FIGURE 5.** Phase trajectories and time series of stochastic system (2) for $\mu = 0.004$ with $\varepsilon = 0.8$ (red) and $\varepsilon = 1.2$ (blue).

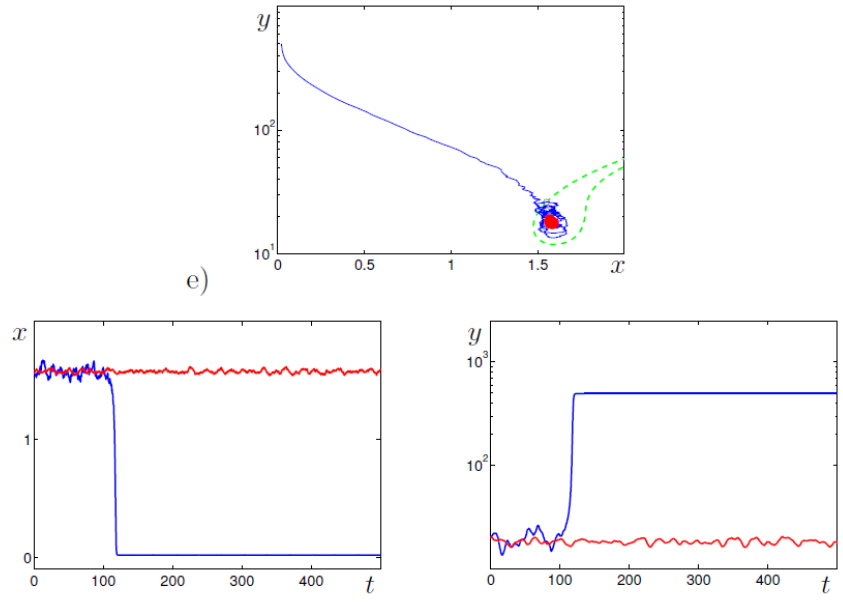


**FIGURE 6.** Phase trajectories and time series of stochastic system (2) for $\mu = 0.013$ with $\varepsilon = 0.01$ (red) and $\varepsilon = 0.03$ (blue).

$E$. For larger noise ($\varepsilon = 0.2$, blue colour), the random trajectory crosses the separatrix shown by green dashed and transits to $D$-basin where continues to oscillated near $D$ ("dormant tumor"). So, due to the transition from $E$ to $D$, the density of the tumor cells decreases and the phenomenon of the noise-induced suppression of the tumor activity is observed.

In Figure 4, stochastic trajectories are shown for system (2) with $\mu = 0.003$ and $\varepsilon = 0.2$ (red), $\varepsilon = 0.4$ (blue). As can be seen, here the phenomenon of the noise-induced suppression of the tumor is observed for larger noise

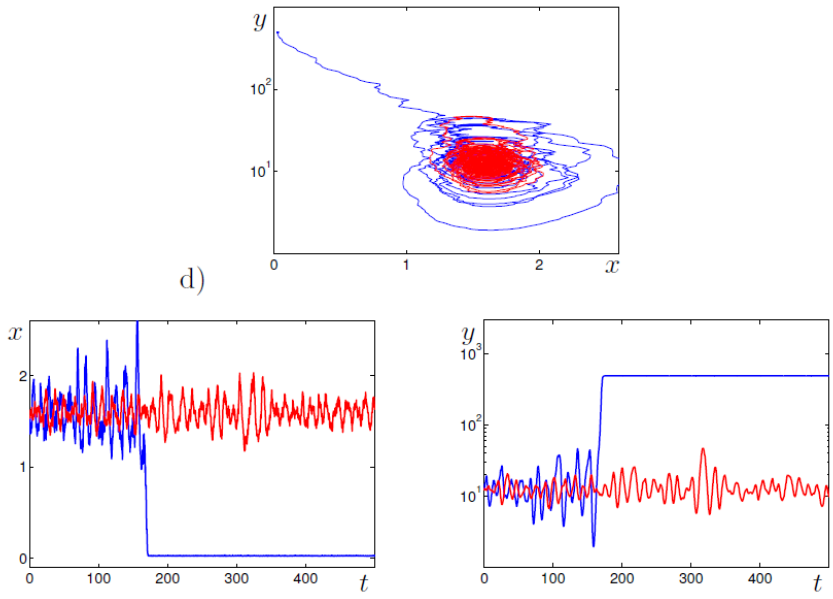


**FIGURE 7.** Phase trajectories and time series of stochastic system (2) for $\mu = 0.01$ with $\varepsilon = 0.1$ (red) and $\varepsilon = 0.2$ (blue).

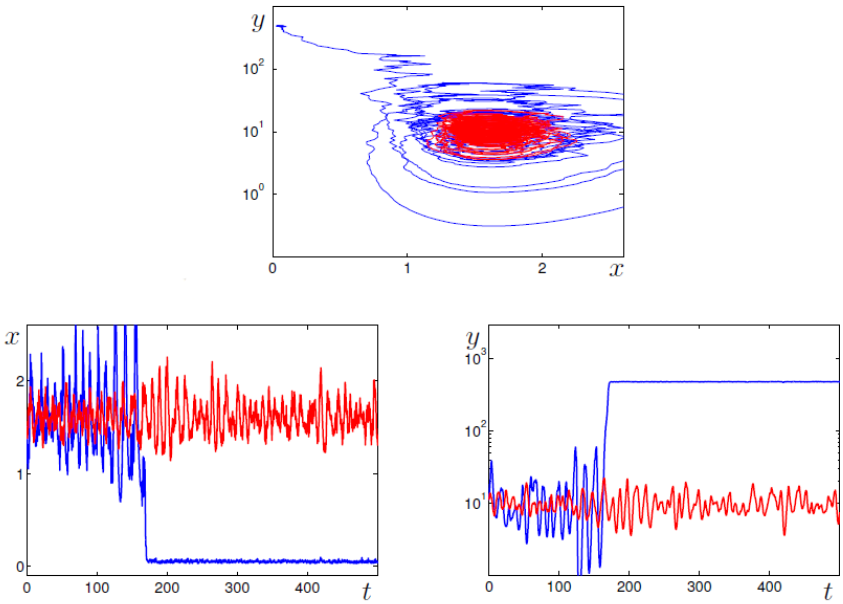


**FIGURE 8.** Phase trajectories and time series of stochastic system (2) for $\mu = 0.006$ with $\varepsilon = 0.2$ (red) and $\varepsilon = 0.4$ (blue).

intensities. This fact can be explained by the following. As parameter $\mu$ increases, the size of $E$-basin increases too, so the stronger noise is required to exit from the $E$-basin.

In Figure 5, stochastic trajectories are plotted for $\mu = 0.004$ and $\varepsilon = 0.8$ (red), $\varepsilon = 1.2$ (blue). Here, the other stochastic phenomenon is demonstrated. Fro strong noise, system (2) exhibits a "trigger" regime of the alternating transitions between $D$- and $E$-basins. Such bimodal oscillations have long phases of small-amplitude oscillations near $E$ and short phases of spike-type jumps to $D$-basin.

Consider now the influence of noise on the right part of the bistability interval $\mu_1 < \mu < \mu_2$.

In Figure 6 for $\mu = 0.013$, two solutions of system (2) starting from the equilibrium $D$ ("dormant tumor") are plotted for $\varepsilon = 0.01$ (red color) and $\varepsilon = 0.03$ (blue color). As can be seen, near the bifurcation point $\mu_2 = 0.01323$, the $D$-basin is small enough, and random trajectories are kept by system near $D$ only for weak noise $\varepsilon = 0.01$. For noise with the intensity $\varepsilon = 0.03$, random trajectory crosses the separatrix shown by green dashed and transits to $E$-basin and stabilizes near the equilibrium $E$. Here, the phenomenon of the noise-induced excitement of the tumor activity is observed.

As the parameter $\mu$ moves to the left from the bifurcation point $\mu_2$, the onset of the phenomenon of noise-induced tumor excitement requires more strong noise (compare Figure 6 with Figure 7 for $\mu = 0.01$ and Figure 8 for $\mu = 0.006$.)

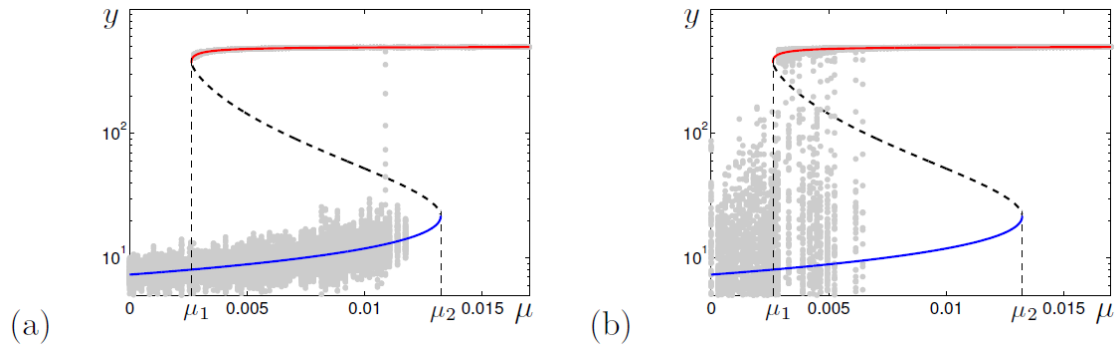


**FIGURE 9.** Random states of stochastic system (2) versus parameter $\mu$ for (a) $\varepsilon = 0.1$, (b) $\varepsilon = 0.5$. Deterministic attractors are the same as in Figure 1.

A general overview of the influence of noise on attractors of tumor-immune system for the whole $\mu$-zone is done in Figure 9. Here, for two values of the noise intensity, a dispersion of random states is shown versus $\mu$. In numerical simulations, we skipped the transient $T = 100$ and plotted $y$-coordinates of system (2) solutions in the time interval $[100, 200]$. In Figure 9, deterministic equilibria from the Figure 1 are also shown. As one can see, increasing noise squeezes the hysteresis zone and transforms the bistability of the deterministic system with the separate stable equilibria $D$ and $E$ to the mixed bimodal stochastic oscillations between $D$ and $E$. It could be also noted that $\mu$-zone of these stochastic bimodal oscillations is localized in the left part of the interval $\mu_1 < \mu < \mu_2$.

## Conclusion

In this paper, we studied the model describing the corporate dynamics of tumor and immune cells. In this model, two regimes of "dormant tumor" and "tumor explosion" correspond to two coexisting stable equilibria. In these circumstances, random noise can transit system from "dormant tumor" to "tumor explosion" and back. It was shown that the analysis of such transitions requires taking into account the mutual arrangement and size of the basins of attraction, a location of separatrices, and the noise intensity. Based on the numerical simulations, we described three scenarios of noise-induced transitions were studied: (i) from "dormant tumor" to "tumor explosion", (ii) from "tumor explosion" to "dormant tumor", (iii) oscillations between these two regimes. For parametric analysis and prediction of these scenarios, the development of analytical approaches is an important theoretical task. Here, mathematical apparatus of the stochastic sensitivity [9, 10, 11, 12, 13] can be useful not only for the analysis but also for the solution of control problems [14].

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